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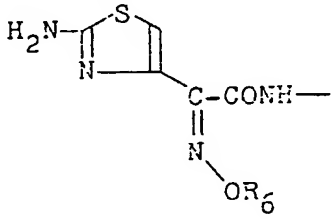
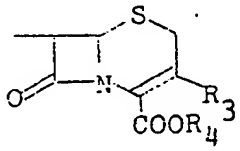
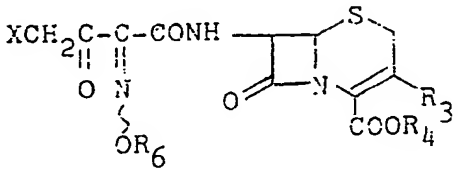
(54) Producing cephalosporins

(57) A 7-[2-(2-aminothiazol-4-yl)-2-(syn)-alkoxyiminoacetamido]cephalosporin derivative of the formula:





wherein R_3 represents $-CH_2R_5$ (R_5 is a hydrogen atom or the residue of a nucleophilic compound), a halogen atom, an alkoxyl group, thiol group, amino group or  -Z (Z is hydrogen atom or hydroxyl, amino, thiol or a hydrocarbon group which may be substituted), $-COOR_4$ represents a carboxylic group which may be esterfied and R_6 represents an alkyl group, or a salt thereof is prepared by reacting a novel 7-(4-halogeno-3-oxo-2-alkoxyiminobutyrylamino) cephalosporin derivative of the formula:



wherein X represents a halogen atom and other symbols have the same meanings as defined above, or a salt thereof with thiourea; the halo reactant is made by acylating the corresponding 7-amino-cephalosporin.

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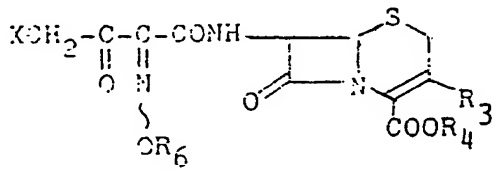
SPECIFICATION

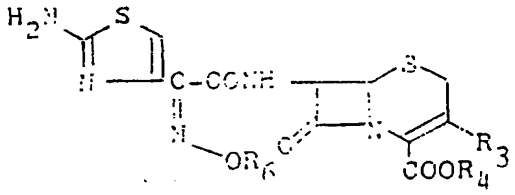
Producing cephalosporins

This invention relates to a 7-(4-halogeno-3-oxo-2-alkoxyiminobutyrylamino) cephalosporin derivative of the formula (I):



(I)

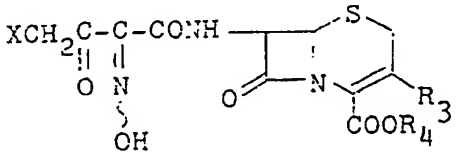
wherein X represents a halogen atom, R_3 represents $-CH_2R_5$ (R_5 is hydrogen atom or the residue of a nucleophilic compound), a halogen atom, an alkoxyl group, thiol group, amino group or  (Z is hydrogen or hydroxyl amino, thiol or a hydrocarbon group which may be substituted), $-COOR_4$ represents a carboxylic group which may be esterified, and R_6 represents an alkyl group, intermediary compounds therefor, salts thereof and also to process for preparing a 7-[2-(2-aminothiazol-4-yl) -2-(syn)-alkoxyiminoacetamido] cephalosporin derivatives of the formula (II):



(II)

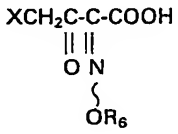
wherein the symbols have the same meanings as defined above, which comprises reacting the above compound (I) with thiourea.

The present inventors, after extensive research, have found that the novel 7-(-4-halogeno-3-oxo-2-alkoxyiminobutyrylamino)cephalosporin derivative or a salt thereof represented by the above formula (I) can be prepared by alkylating a 7-(4-halogeno-3-oxo-2- hydroxyiminobutyrylamino) cephalosporin derivative of the formula (III):



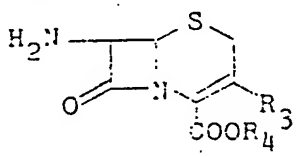
(III)

wherein the symbols have the same meanings as defined above, or a salt thereof, or reacting a novel 4-halogeno-3-oxo-2- alkoxyiminobutyric acid of the formula (IV):



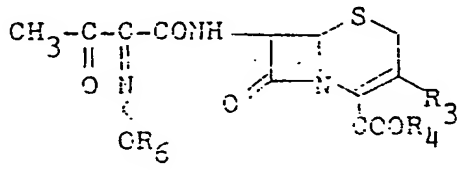
(IV)

wherein the symbols have the same meanings as defined above, or a reactive derivative thereof with a 7-amino-cephalosporin derivative of the formula (V):



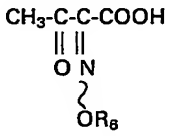
(V)

wherein the symbols have the same meanings as defined above, or a salt thereof, or halogenating a novel compound of the formula (VII):



(VII)

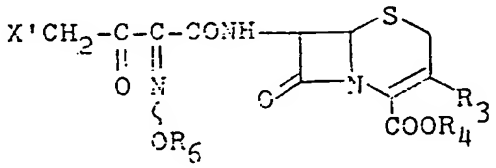
wherein the symbols have the same meanings as defined above, or a salt thereof, the compound (VII) or a salt thereof being obtained by reacting the novel 3-oxo-2-alkoxyiminobutyric acid of the formula (VI):



(VI)

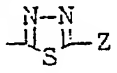
wherein the symbol has the same meaning as defined above, or a reactive derivative thereof with a compound (V) or a salt thereof, and also found that the derivative (II) having excellent antibacterial activity can be prepared in a good yield by reacting a compound (I) thus prepared or a salt thereof with thiourea.

That is, the present invention provides the cephalosporin derivative of the formula (I'):



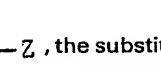
(I')

wherein X' represents hydrogen atom or a halogen atom, and other symbols have the same meanings as defined above, or a salt thereof and a process for producing a 7-[2-(2-aminothiazol-4-yl) -2-(syn)-alkoxyiminoacetamido] cephalosporin derivative or a salt thereof, which comprises reacting the compound (I) or a salt thereof with thiourea.

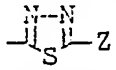
In the formulas (I), (III) and (IV), X represents a halogen atom such as chlorine, bromine, fluorine or iodine. Among them, chlorine or bromine is usually frequently used. The symbol R_3 on the cephem ring in the formulas (I), (II), (III), (IV), (V) and (VII) represents $-CH_2R_5$ (R_5 is hydrogen atom or the residue of a nucleophilic compound), a halogen atom, an alkoxyl group, thiol group, amino group or 

(Z is hydrogen atom or hydroxyl amino, thiol or a hydrocarbon group which may be substituted). The symbol R_5 herein used represents hydrogen atom or a residue of a nucleophilic compound. As the residue of a nucleophilic compound represented by R_5, there may be mentioned, for example, hydroxyl group, mercapto group, lower aliphatic acyloxy group having 2 to 4 carbon atoms which may be substituted such as acetyloxy group, propionyloxy group, 3-oxobutyryloxy group, 3-carboxypropionyloxy group, 3-ethoxycarbamoylpropionyloxy group, 4-carboxybutyryloxy group, etc., aromatic acyloxy group which may be substituted such as mandelyloxy group, 2-carboxybenzoyloxy group, 2-(carboethoxycarbamoyl) benzoyloxy group, 2-carboethoxysulfamoyl) benzoyloxy group, etc., carbamoyloxy group, cyano, azide, amino, carbamoylthio, thiocarbamoyloxy, carbamoyloxy group of which amino group is protected (e.g. N-mono-, di- and tri-halogenoacetyl carbamoyl group such as N-chloro-acetyl carbamoyloxy group, N-dichloroacetyl carbamoyloxy group, N-trichloroacetyl carbamoyloxy group, etc., N-chlorosulfonyl carbamoyloxy group, N-trimethylsilyl carbamoyloxy group), and phenylglycyloxy group. These residues of the nucleophilic compounds may also be substituted by substituents, which are generally 1 to 2 in number, such as alkyl groups (e.g. lower alkyl group having 1 to 3 carbon atoms, such as methyl, ethyl or propyl), or acyl groups (e.g. lower aliphatic acyl groups having 2 to 4 carbon atoms such as acetyl, propionyl or butyryl; aromatic acyl groups such as benzoyl, p-chloro-benzoyl, p-methylbenzoyl, mandeloyl, etc.). Alternatively, the residue R_5 of a nucleophilic compound may be quaternary ammonium group, or the residue R_5 of a nucleophilic compound may be a heterocyclic ring bonded through sulfur, namely a heterocyclicthio group. The heterocyclic ring herein mentioned refers to a 5- to 6-membered ring containing 1 to 4 hetero atoms selected from oxygen, sulfur or nitrogen wherein the nitrogen atom may be in the form of oxide. As these heterocyclic ring, there may frequently be used pyridyl, N-oxide pyridyl, pyrimidyl, pyridazinyl, N-oxide pyridazinyl, pyrazolyl, diazolyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, oxazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1.3,4-oxadiazolyl, 1.2,5-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H-tetrazolyl, 2H-tetrazolyl or the like. These heterocyclic rings may have substituents on the ring, including lower alkyl groups having 1 to 3 carbon atoms such as methyl, ethyl or propyl, lower alkoxy

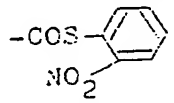
groups have 1 to 3 carbon atoms such as methoxy, ethoxy or propoxy, halogen atoms such as chlorine or bromine, tri-halogeno-substituted lower alkyl such as trifluoromethyl or trichloroethyl, hydroxyl group, mercapto group, amino group, carboxylic group, carbamoyl group, di-lower alkylamino lower alkyl group having 1 to 3 carbon atoms such as dimethylaminoethyl or dimethyl-aminomethyl, carboxymethyl, and so on. When these substituents are substituted on the heterocyclic ring, the number of these substituents is generally one or two. As the quaternary ammonium group represented by R_5, there may frequently be used pyridinium, 3-methylpyridinium, 4-methylpyridinium, 3-chloropyridinium, 3-bromopyridinium, 3-iodopyridinium, 4-carbamoylpyridinium, 4-(N-hydroxy-methylcarbamoyl) pyridinium, 4-(N-carbomethoxycarbamoyl) pyridinium, 4-(N-cyanocarbamoyl) pyridinium, 4-(carboxymethyl) pyridinium, 4-(hydroxymethyl)pyridinium, 4-(tri-fluoromethyl)pyridinium, quinolinium, picolinium or lutidinium. When R_3 represents a halogen atom, an alkoxyl group, thiol group or an amino group, chlorine or bromine as mentioned above may be used as the halogen atom. Typical examples of alkoxyl groups are methoxy group and ethoxy group. When R_3 represents



, the substituents on hydroxyl group, amino group, thio group or a hydrocarbon group (e.g. alkyl group, preferably having 1 to 4 carbon atoms, such as methyl, ethyl, propyl, iso-butyl or tert-butyl, aralkyl such as benzyl, aryl group such phenyl or naphthyl) represented by Z may be lower alkyl groups, acyl groups, aralkyl groups or aryl groups as mentioned above. These substituents may further be substitued by carboxylic group, sulfo group, hydroxyl group or others. In case of Z being amino group, there may also be included those in which pyrolidino, morpholino or thiomorpholino group is formed together with nitrogen atom. Namely, typical examples of



may include 5-acetylamino-1, 3,4-thiadiazol-2-yl, 5-amino-1, 3, 4-thiadiazol-2-yl, 5-dimethylamino-1, 3,4-thiadiazol-2-yl, 5-methyl-1, 3, 4-thiadiazol-2-yl, 1, 3,4-thiadiazol-2-yl, and the like. The carboxylic group represented by $-COOR_4$ which may be esterified means carboxylic group, an inorganic salt thereof with an alkali or alkaline earth metal salt such as sodium or potassium salt or an organic salt such as triethylamine salt and also a carboxylic group which is esterified. As such esters, there may be used methyl, ethyl, tert-butyl, tert-amyl, benzyl, p-nitrobenzyl, alkanoyloxymethyl (e.g. acetoxymethyl, etc.), di- or tri-alkylsilyl (e.g. trimethylsilyl, etc), alkoxysilyl, benzhydryl, 1-indanyl, phthalidyl, 5-indanyl, phenacyl, phenyl, p-nitrophenyl, alkoxyalkyl (e.g. methoxymethyl, ethoxymethyl, etc.), alkenyl, trichloroethyl, methylsulfonylethyl, benzoylmethyl, benzyloxymethyl, t-butyl, methoxybenzyl, trityl, methylthiomethyl, pivaloyloxymethyl, α-acetoxybutyl, or α-acyloxy-α-substituted methyl-ester such as α-ethoxycarbonyloxy-α-methylmethyl, etc. These esters may preferably be those which can be led to the free form under the mild conditions so as not to cleave the β-lactam ring. For example, there may be used the groups R_4 convertible to hydrogen under mild acidic or alkaline conditions such as diphenylmethyl, a substituted phenyl, a lower alkyl sulfonylethyl or pivaloyloxymethyl, or the groups which can be eliminated by oxidation or reduction reaction such as trichloroethyl group or benzyl group. As the group $-COOR_4$, there may also be included the groups readily hydrolyzable to -COOH such as



As an another salt of compound (II), there is an inorganic acid salt such as hydrochloric acid salt, hydrobromic acid salt, etc.

As the alkyl group represented by R_6 in the formulas (I), (II), (IV), (VI), and (VII), there may be used lower alkyl groups have 1 to 4 carbon atoms such as methyl, ethyl, etc.

The wavy line in the formulas (I), (III), (IV), (VI) and (VII) indicates that the groups OH or OR_6 can be in the position of either one or the other of the two possible configurations *syn* and *anti*, or can be the mixture of the both.

Referring now to the reactions in the present invention, a compound (I) is prepared by alkylating a compound (III). The alkylation reaction is generally conducted in a solvent under ice-cooling or at around room temperature and completed in most cases within several minutes to several hours. There may be employed any solvent which does not interfere with the reaction, for example, tetrahydrofuran, dioxane, methanol, ethanol, chloroform, methylene dichloride, ethyl acetate, butyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, water or a mixture thereof. As alkylating agent, there may be used an alkyl halide such as methyl iodide, methyl bromide, ethyl iodide, ethyl bromide, etc., dimethyl sulfate, diethyl sulfate, diazomethane, diazoethane or methyl p-toluenesulfonate. Except for the case when diazomethane or diazoethane is used, the compound (III) are reacted with the aforesaid alkylating agent in the presence of an alkali metal carbonate such as sodium carbonate, potassium carbonate, etc., an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, etc. or an organic base such as triethylamine, pyridine, dimethylaniline, etc. The thus prepared compound (I) can be purified by isolation according to conventional methods and can also be provided without isolation as the starting material in the subsequent reaction.

The reaction for preparing the compound (II) by reacting the compound (I) with thiourea is generally conducted in a solvent. There may be employed any solvent which does not interfere with the present reaction. Examples of the solvent are water, methanol, ethanol, acetone, tetrahydrofuran, dioxane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpiperidone and mixtures thereof. The reaction is carried out under ice-cooling, at room temperature or under heating. Usually, thiourea is used in an amount of one to several equivalents of the compound (I). The reaction time is from 1 to 48 hours, preferably from 1 to 10 hours. The thus prepared compound (II) can be purified by isolation according to conventional methods such as concentration, concentration under reduced pressure, crystallization, recrystallization, solvent extraction, salting out, fractional distillation, distillation or chromatography.

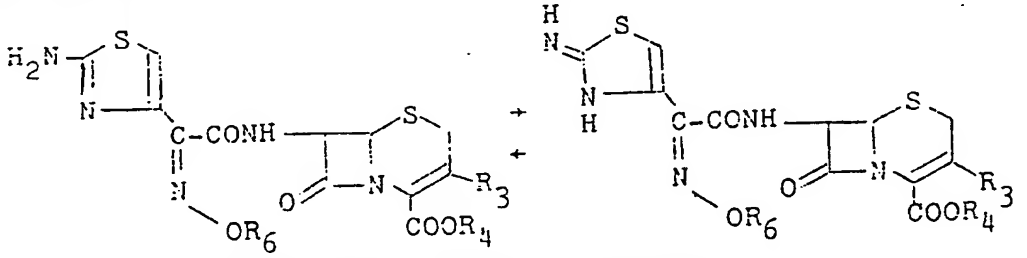
The compound (IV) or the compound (VI) is allowed to react with the 7-aminocephalosporin derivative (V) to give the compound (I) or the compound (VII). The compound (IV) or the compound (VI) is used as acrylating agent of the amino group at 7-position of the compound (V) in the free form or in the form of a reactive derivative thereof. That is, the compound (IV) or (VI) is provided for the acrylating reaction either in the free form or in the form of a reactive derivative thereof such as alkali or alkaline earth metal salt at the carboxylic group (e.g. sodium, potassium, or calcium salt), a salt with an organic amine such as trimethylamine, pyridine, etc., an acid halide thereof (e.g. acid chloride, acid bromide, etc), an acid anhydride, a mixed acid anhydride, an active amide or an activated ester. As the activated ester, there may be used p-nitrophenyl ester, 2,4-dinitrophenyl ester, pentachlorophenyl ester, N-hydroxysuccinimide ester or N-hydroxyphthalimide ester. As a mixed acid anhydride there may be used a mixed acid anhydride with a carbonic acid mono-ester such as mono-methyl carbonate, mono-iso-butyl carbonate, etc. or a mixed acid anhydride with a lower alkanoic acid which may be substituted by halogen atom or atoms such as pivalic acid or trichloroacetic acid. When the compound (IV) or (VI) is used in the form of a free acid or a salt, a suitable condensing agent is to be used. As the condensing agent, there may be used N,N'-di-substituted carbodiimides such as N,N'-dicyclohexyl carbodiimide, azolide compounds such as N,N'-carbonyl di-imidazole or N,N'-thionyl di-imidazole, dehyrating agents such as N-ethoxycarbonyl-2-ethoxy-1, 2-dihydroquinoline, phosphorus oxychloride or alkoxy acetylene, 2-halogenopyridinium salts (e.g. 2-chloropyridiniummethyl iodide, 2-fluoro-pyridiniummethyl iodide, etc.) and so forth. When the condensing agent is used, the reaction is considered to proceed via the reactive derivative of the compound (IV) or (VI). The reaction is generally conducted in a suitable solvent. As such a solvent, there may frequently be used a halogenated hydrocarbon such as chloroform, methylene dichloride, etc., an ether such as tetrahydrofuran, dioxane, etc., dimethylformamide, dimethylacetamide, acetone, water or a mixture thereof. The compound (IV) or (VI) is generally used in amount of about 1 to several moles per one mole of the compound (V). The reaction is carried out generally in the range from -50 to 40°C. The reaction time is usually from 10 minutes to 48 hours, preferably from 30 minutes to 10 hours. The thus prepared compound (I) is isolated by conventional methods as described above. The compound (VII) may similarly be isolated by conventional methods, but also be provided for use as the starting material in the subsequent step.

The reaction conventionally used for halogenation of active hydrogen in organic chemistry may be applied to the reaction in which the compound (VI) or (VII) is halogenated to be converted to the compound (IV) or (I). As a halogenating agent, there may be employed, for example, chlorine, bromine, surfuryl chloride, etc. The reaction may sometimes proceed smoothly in a solvent. As such a solvent, there may be used chloroform, methylene chloride, dichloroethane, dichloroethylene, carbon tetrachloride, acetic acid, benzene, toluene, etc. The reaction may be carried out under ice-cooling or under heating but usually at a temperature in the range from 0 to 60°C. The reaction time is generally from 5 minutes to 48 hours, preferably from 10 minutes to 10 hours. The resultant compound (IV) or (I) may be subjected to isolation purification by conventional methods, respectively. The compound (IV) may be provided for use as the starting material for the reaction with the compound (V) in the form of the reaction mixture as it is without isolation.

Among the starting compounds to be used in the present invention, the esters of 3-oxo-2-alkoxyimino butyric acid represented by the formula (VI) are disclosed in, for example, J.Indian Chem. Soc., *42*, 677 (1965); J.Am. Chem. Soc., *60*, 1328 (1938). The compound (VI) can be prepared by eliminating the ester groups from the corresponding esters under conventional conditions for ester hydrolysis. Usually, the compound (VI) is used as the starting material without purification for preparation of the compound (IV) or (VII). The other compound (III) can be prepared according to the method disclosed in Chem. Pharm. Bull., *25*, 3117 (1977) or a method similar thereto. The 7-amino-cephalosporin derivative as represented by the formula (V) can be prepared according to the methods as disclosed in German laid-open patent application No. 461478, German laid-open patent application No. 2607064, German laid-open patent application No. 2619243, Japanese published unexamined patent application No. 52083/1975 (corresponding to British patent 1453049 and German laid-open patent application No. 2439880), German laid-open patent applications No. 2460331 and No. 2460332, Japanese published unexamined patent application No. 138696/1976, (corresponding to German laid-open patent application No. 2620094), No. 129590/1975 (corresponding to British patent 1503581 and German laid-open patent application No. 2506330), No. 95485/1975 (corresponding to U.S. patent 4013651, and German laid-open patent application No. 2620308), and No. 108087/1976 (corresponding to German laid-open patent application No. 2606192), J.Am. Chem. Soc., *96*, 4986 (1974), Helv. Chim. Acta, *57*, 1919 (1974), ibid. *57*, 2044 (1974), ibid. *55*, 423 (1972), ibid. *58*, 2437 (1975), J. Am. Chem. Soc., *98*, 2342 (1976), Helv. Chim. Acta, *55*, 408 (1972), British patent 137761, German laid-open patent application No. 2151567, and so on, or methods similar to these methods.

The thus prepared compounds (IV) and (VI) are excellent intermediary compounds for the useful novel compounds, and the compounds (I) and (VII) are *per se* novel cephalosporin derivatives having anti-bacterial activity which can be advantageous intermediary compounds for synthesis of the compound (II).

The cephalosporin derivative represented by the formula (II) is considered to have the structure of tautomeric isomers of 2-aminothiazole isomer and 2-iminothiazoline isomer:



For convenience, the compound (II) is set forth in the form of the thiazole type.

Typical examples of the compound (I) prepared according the present invention are set forth below:

7-(4-bromo-3- oxo-2-methoxyiminobutyrylamino)-3- (1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem-4-carboxylic acid;

7-(4-chloro-3-oxo-2- methoxyiminobutyrylamino) -3-(1-methyl-1H-tetrazol-4-yl) thiomethyl-3-cephem-4-carboxylic acid;

7-(4-bromo-3-oxo-2- methoxyiminobutyrylamino)- 3-(1-methyl-1H- tetrazol-5-yl) thiomethyl-3-cephem-4-carboxylic acid benzhydryl ester;

7-(4-bromo-3-oxo-2-ethoxyiminobutyrylamino) cephalosporanic acid;

7-(4-bromo-3-oxo- 2-ethoxyiminobutyrylamino) cephalosporanic acid t-butyl ester;

7-(4-chloro-3-oxo- 2-methoxyiminobutyrylamino) cephalosporanic acid;

7-(4-bromo-3-oxo-2- methoxyiminobutyrylamino) cephalosporanic acid;

7-(4-chloro-3-oxo-2-methoxyiminobutyrylamino)-3-(2- methyl-1, 3, 4-thiadiazol,5-yl) thiomethyl-3-cephem-4-carboxylic acid;

7-(4-chloro-3-oxo-2-methoxyiminobutyrylamino) -3-[1-(2-N,N-dimethylaminoethyl)- 1H-tetrazol-5-yl] thiomethyl-3-cephem-4-carboxylic acid;

7-(4-bromo-3-oxo-2-methoxyiminobutyrylamino)-3- carbamoyloxymethyl-3-cephem -4-carboxylic acid;

7-(4-chloro-3-oxo-2-methoxyiminobutyrylamino) -3-carbamoyloxymethyl-3- cephem-4-carboxylic acid;

7-(4-bromo-3-oxo- 2-methoxyiminobutyrylamino) desacetoxy cephalosporanic acid;

7-(4-bromo-3-oxo-2-methoxyiminobutyrylamino) -3-(5-acetamido-1, 3, 4-thiadiazol-2-yl) -3-cephem-4-carboxylic acid;

7-(4-chloro-3-oxo-2- methoxyiminobutyrylamino)-3- (5-methyl-1, 3, 4-thiadiazol-2-yl) -3-cephem-4-carboxylic acid;

7-(4-bromo-3-oxo-2-methoxyiminobutyrylamino) -3-(1,3,4-thiadiazol-2-yl) -3-cephem-4-carboxylic acid;

7-(4-bromo-3-oxo-2 methoxyiminobutyrylamino)-3- (5-dimethylamino-1,3,4- thiadiazol-2-yl), -3-cephem-4-carboxylic acid;

7-(4-bromo-3-oxo-2-methoxyiminobutyrylamino) -3-(5-N-methylacetamido-1,3,4- thiadiazol-2-yl) -3-cephem-4-carboxylic acid;

7-(4-chloro-3-oxo-2-methoxyiminobutyrylamino) -3-chloro-3-cephem-4-carboxylic acid;

7-(4-bromo-3-oxo-2methoxyiminobutyrylamino) -3-methoxy-3-cephem-4-carboxylic acid;

7-(4-chloro-3-oxo-2-methoxyiminobutyrylamino)- 3-methoxy-3-cephem-4-carboxylic acid;

7-(4-bromo-3-oxo-2-methoxyiminobutyrylamino)- 3-methylthio-3-cephem-4- carboxylic acid; and so on.

Typical examples of the compounds prepared according to the process of the present invention are set forth below:

7-(3-oxo-2-methoxyiminobutyrylamino) -3-(1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem -4-carboxylic acid;

Sodium 7-(3-oxo-2-methoxyiminobutyrylamino)- 3-(1-methyl-1H-tetrazol-4-yl) thiomethyl -3-cephem-4-carboxylate;

7-(3-oxo-2-methoxyiminobutyrylamino) -3-(1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem-4- carboxylic acid benzhydryl ester;

7-(3-oxo-2-ethoxyiminobutyrylamino) cephalosporanic acid;

7-(3-oxo-2-ethoxyiminobutyrylamino) cephalosporanic acid t-butyl ester;

7-(3-oxo-2-methoxyiminobutyrylamino) cephalosporanic acid;

Sodium 7-(3-oxo-2-methoxyiminobutyrylamino) cephalosporanate;

7-(3-oxo-2-methoxyiminobutyrylamino) -3-(2-methyl-1, 3, 4-thiadiazol-5-yl) thiomethyl-3-cephem-4-carboxylic acid;

7-(3-oxo-2-methoxyiminobutyrylamino)-3- [1-(2-N,N-dimethylaminoethyl) -1H-tetrazol-5-yl] thiomethyl-3-cephem-4-carboxylic acid;

7-(3-oxo-2-methoxyiminobutyrylamino) -3-carbamoyloxymethyl-3-cephem-4- carboxylic acid;

Sodium 7-(3-oxo-2-methoxyiminobutyrylamino)-3-carbamoyloxymethyl-3-cephem-4- carboxylate;

7-(3-oxo-2-methoxyiminobutyrylamino) desacetoxy cephalosporanic acid;
7-(3-oxo-2-methoxyiminobutyrylamino)-3-(5-acetamido-1, 3, 4-thiadiazol-2-yl) -3-cephem-4-carboxylic acid;
7-(3-oxo-2-methoxyiminobutyrylamino) -3-(5-methyl-1, 3, 4-thiadiazol-2-yl) -3-cephem-4-carboxylic acid;
7-(3-oxo-2-methoxyiminobutyrylamino) -3-(1,3,4-thiadiazol-2-yl) -3-cephem-4-carboxylic acid;
7-(3-oxo-2-methoxyiminobutyrylamino) -3-(5-dimethylamino-1, 3, 5-thiadiazol-2-yl) -3-cephem-4-carboxylic acid;
7-(3-oxo-2-methoxyiminobutyrylamino) -3-(5-N-methylacetamido-1, 3,4-thiadiazol-2-yl) 3-cephem-4-carboxylic acid;
7-(3-oxo-2-methoxyiminobutyrylamino) -3-chloro-3-cephem-4-carboxylic acid;
7-(3-oxo-2-methoxyiminobutyrylamino) -3-methoxy-3-cephem-4-carboxylic acid;
7-(3-oxo-2-ethoxyiminobutyrylamino)-3-methoxy-3cephem-4-carboxylic acid;
7-(3-oxo-2-methoxyiminobutyrylamino) -3-methyl-thio-3-cephem-4- carboxylic acid; and so on.

Typical examples of the compound (IV) are as follows:
4-bromo-3-oxo-2-methoxyiminobutyric acid;
4-chloro-3-oxo-2-methoxyiminobutyric acid;
4-bromo-3-oxo-2-ethoxyiminobutyric acid;
4-chloro-3-oxo-2-ethoxyiminobutyric acid;
and so on.

Example 1

Methyl 3-oxo-2-methoxyiminobutyrate (20.3 g) is dissolved in 100 ml of methanol and to this solution is added dropwise 200 ml of 1N-aqueous sodium hydroxide solution over about 30 minutes under stirring. There is slight heat generation during said addition. After the dropwise addition, the mixture is further continued to be stirred at room temperature for one hour. Then, methanol is evaporated under reduced pressure and the residue is washed with ethyl acetate. The aqueous layer is adjusted to pH 2.0 with 3N-hydrochloric acid under ice-cooling, mixed with sodium chloride and subjected to extraction with ethyl acetate. The ethyl acetate extract is dried over magnesium sulfate and thereafter concentrated to give crude 3-oxo-2-methoxyiminobutyric acid as viscous oily product, which is further subjected to recrystallization from chloroform-n-hexane to obtain colorless crystals. 16.0 g.

Melting poing : 81 - 82°C.

NMR($CDCl_3$): 2.40 ppm(3H,s, CH_3CO), 4.10 ppm (3H, s, OCH_3), 10.87 ppm (1H, s, COOH)

Elemental analysis for $C_5H_7NO_4$:

Calculated: C 41.38; H 4.86; N 9.65

Found: C 41.71; H 4.87; N 9.49

Example 2

To a solution of 1.87 g of ethyl 3-oxo-2-ethoxyiminobutyrate in 80 ml of methanol is added drop-wise 40 ml of 1N-aqueous sodium hydroxide solution. After completion of the dropwise addition, the mixture is stirred at room temperature for one hour, and the mixture is treated in the same manner as in Example 1 to give crude product of 3-oxo-2-ethoxyiminobutyric acid as colorless crystals. 1.3 g.

NMR($CDCl_3$)- 1.35 ppm (3H, t, $CH_2C\underline{H}_3$), 2.42 ppm (3H, s, CH_3CO), 4.40 ppm (2H, q, $C\underline{H}_2CH_3$), 7.82 ppm (1H, s, COOH).

Example 3

To a solution of 590 mg of 3-oxo-2-ethoxy-iminobutyric acid in 10 ml of methylene chloride is added dropwise a solution of 640 mg of bromine in 5 ml of methylene chloride. The resultant mixture is stirred at 40°C for 30 minutes. The reaction mixture is washed with ice-water, followed by concentration under reduced pressure, to give crude product of 4-bromo-3-oxo-2-ethoxyiminobutyric acid. 750 mg.

NMR($CDCl_3$): 1.40 ppm (3H, t, $CH_2C\underline{H}_3$), 4.37 ppm (2H, s, $BrCH_2$), 4.45 ppm(2H, q, $C\underline{H}_2CH_3$)

Example 4

To a solution of 7.0 g of 3-oxo-2-methoxy-iminobutyric acid in 50 ml of methylene chloride is added dropwise a small amount of a solution of 7.71 g of bromine in 10 ml of methylene chloride. The mixture is heated in a water bath at 50°C and, when the color of bromine begins to disappear, the water bath is removed and the residual bromine solution is added dropwise to the mixture at room temperature at such rate that the color of bromine disappears. After the dropwise addition, when the color of bromine has disappeared, stirring is stopped and the resultant mixture is concentrated under reduced pressure to give crude 4-bromo-3-oxo-2-methoxyiminobutyric acid as oily product. 11.1g.

NMR($CDCl_3$): 4.17 ppm (3H, s, OCH_3), 4.37 ppm (2H, s, $BrCH_2$).

Example 5

To a solution of 320 mg of 3-oxo-2-ethoxy-iminobutyric acid in 10 ml of methylene chloride is added dropwise a solution of 400 mg of bromine in 3 ml of methylene chloride and the resultant mixture is stirred at room temperature for 2 hours. Then, 500 mg of phosphorus pentachloride is added to the reaction mixture

and the mixture is stirred at room temperature for one hour to obtain a solution of 4-bromo-3-oxo-2-ethoxyiminobutyric acid chloride in methylene chloride. On the other hand, a solution of 660 mg of t-butyl 7-aminocephalosporanate and 500 mg of pyridine in 10 ml of methylene chloride is cooled to -30°C and, while stirring the solution at said temperature, the above acid chloride solution is added dropwise thereto within about 15 minutes. After completion of the dropwise addition, the mixture is warmed to room temperature, at which the mixture is stirred for 2 hours, and then concentrated under reduced pressure. The residue is dissolved in ethyl acetate and the ethyl acetate layer is washed with 3N-hydrochloric acid, followed by washing with water, then with 5% aqueous sodium hydrogen carbonate solution and further with water, and dried. The semi-solid obtained after evaporation of ethyl acetate is purified by chromatography on silica gel to give t-butyl 7-(4-bromo-3-oxo-2-ethoxyiminobutyrylamino) cephalosporanate as foamy solid. 620 mg.

NMR($CDCl_3$): 1.36 ppm (3H, t, $CH_2C\underline{H}_3$, 1.50 ppm (9H, s, $-C(CH_3)_3$), 2.05 ppm (3H, s, CH_3CO), 3.44 ppm (2H, q, 2-CH_2), 4.37 ppm (2H, q, $C\underline{H}_2CH_3$), 4.55 ppm (2H, s, $BrCH_2$), 4.90 ppm (2H, q, 3-CH_2), 4.99 ppm (1H, d, 6-H), 5.83 ppm (1H, dd, 7-H), 7.12 ppm (1H, d, CONH).

Example 6

To a solution of 200 mg of t-butyl 7-(4-bromo-3-oxo-2-ethoxyiminobutyrylamino) cephalosporanate in 5 ml of ethanol is added 100 mg of thiourea and the mixture is stirred at room temperature for 2 hours. After evaporation of ethanol under reduced pressure, ethyl acetate and water are added to the residue. After shaking the mixture, the ethyl acetate layer is washed with water and dried. The oily product obtained after evaporation of ethyl acetate is purified by chromatography on silica gel to give t-butyl 7-[2-(2-aminothiazol-4-yl)-2-(syn)-ethoxyiminoacetamido] cephalosporonate as foamy solid. 152 mg.

NMR($CDCl_3$): 1.22 ppm (3H, t, $CH_2C\underline{H}_3$), 1.43 ppm (9H, s, $C(CH_3)_3$), 1.97 ppm (3H, s, CH_3COO), 3.36 ppm (2H, q, 2-CH_2), 4.19 ppm (2H, q, $C\underline{H}_2CH_3$), 4.82 ppm (2H, q, 3-CH_2), 4.93 ppm (1H, d, 6-H), 5.55 ppm (2H, bs, NH_2), 5.86 ppm (1H, dd, 7-H), 6.74 ppm (1H, s, thiazole 5-H), 7.32 ppm (1H, d, CONH).

Example 7

3-oxo-2-methoxyiminobutyric acid (290 mg) is dissolved in 10 ml of methylene chloride. To the resultant solution is added a solution of 320 mg of bromine in 1 ml of methylene chloride and the mixture is stirred at room temperature for one hour. Then, 500 mg of dicyclohexylcarbodiimide and 495 mg of benzhydryl 7-amino-3- (1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem-4-carboxylate are added to the reaction mixture and the mixture is stirred at room temperature for 3 hours. After evaporation of methylene chloride under reduced pressure, ethyl acetate is added to the residue. The insolubles are filtered off and the filtrate is washed with 5% aqueous sodium hydrogen carbonate solution, and then with water, followed by drying. The oily product obtained after evaporation of ethyl acetate is purified by chromatography on silica gel to give benzhydryl 7-(4-bromo-3-oxo-2-methoxyiminobutyryl-amino) -3-(1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem-4-carboxylate. 480 mg.

NMR($CDCl_3$): 3.70 ppm (2H, s, 2-CH_2), 3.80 ppm (3H, s, N-CH_3), 4.11 ppm (3H, s, OCH_3), 4.29 ppm (2H, q, 3-CH_2), 4.53 ppm (2H, s, $BrCH_2$), 4.99 ppm (1H, d, 6-H), 5.85 ppm (1H, dd, 7-H), 6.88 ppm (1H, s, $C\underline{H}(C_6H_5)_2$).

7.31 ppm (10H, s, $(C_6H_5)_2$).

Example 8

After dissolving 610 mg of benzhydryl 7-(4-bromo-3-oxo-2-methoxyiminobutyrylamino) -3-(1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem-4-carboxylate in a mixture of 20 ml of ethanol and 10 ml of tetrahydrofuran, 304 mg of thiourea is added to the solution and the resultant mixture is stirred at room temperature for 2 hours. The solvent is then evaporated under reduced pressure and the residue is dissolved in ethyl acetate, washed with water and then dried. The residue obtained by evaporation of ethyl acetate is purified by chromatography on silca gel to give benzhydryl 7-[2-(2-amino-thiazol-4-yl) -2-(syn)-methoxyiminoacetamido] -3-(1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem-4-carboxylate. 540 mg.

NMR($CDCl_3$): 3.70 ppm (2H, s, 2-CH_2), 3.78 ppm (3H, s, N-CH_3), 3.97 ppm (3H, s, OCH_3), 4.28 ppm (2H, q, 3-CH_2), 5.02 ppm (1H, d, 6-H), 5.97 ppm (1H, dd, 7-H), 6.77 ppm (1H, s, thiazole 5-H), 6.90 ppm (1H, s, $C\underline{H}(C_6H_5)_2$).

7.31 ppm (10H, s, $(C_6H_5)_2$).

7.77 ppm (1H, d, CONH).

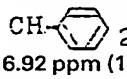
This product (50 mg) is added to a mixture of 0.5 ml of anisole and 2.5 ml of trifluoroacetic acid. After stirring the mixture at room temperature for 30 minutes, anhydrous ether is added thereto and the resulting precipitates are collected by filtration. The precipitates are dissolved in a small amount of 5% aqueous sodium hydrogen carbonate solution and the solution is passed through a column packed with Sephadex LH-20 (registered trade mark: Pharmacia Fine Chemicals Co., Sweden) to give 35 mg of purified sodium

7-[2-(2-aminothiazol-4-yl) -2-(syn)-methoxyiminoacetamido]-3-(1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem-4-carboxylate.

NMR(D_2O): 3.59 ppm (2H, q, 2-CH_2), 3.93 ppm (3H, s, OCH_3), 3.98 ppm (3H, s, N-CH_3), 4.08 ppm (2H, q, 3-CH_2), 5.12 ppm (1H, d, 6-H), 5.72 ppm (1H, d, 7-H), 6.93 ppm (1H, s, thiazole, 5-H).

Example 9

A mixture of 250 mg of phosphorus pentachloride with a solution of 145 mg of 3-oxo-2-methoxyiminobutyric acid in 10 ml of methylene chloride is stirred at room temperature for one hour to obtain a solution of 3-oxo-2-methoxyininobutyric acid chloride. On the other hand, a solution of 495 mg of benzhydryl 7-amino-3- (1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem- 4-carboxylate and 240 mg of pyridine in 10 ml of methylene chloride is cooled to -30°C, at which the above acid chloride solution is added dropwise thereto within about 20 minutes. After completion of the dropwise addition, the mixture is stirred at room temperature for 2 hours and then mixed with 100 ml of ethyl acetate. The mixture is washed with water, 1N-hydrochloric acid, water, 5% aqueous sodium hydrogen carbonate solution and then with water, followed by drying. The residue obtained by evaporation of the solvent is subjected to purification by silica gel chromatography to give benzhydryl 7-(3-oxo-2- methoxyiminobutyrylamino) -3-(1-methyl-1H-tetrazol-5-yl) thiomethyl-3-cephem -4-carboxylate. 440 mg.

NMR($CDCl_3$): 2.38 ppm (3H, s, CH_3CO), 3.72 ppm (2H, s, 2-CH_2), 3.80 ppm (3H, s, N-CH_3), 4.10 ppm (3H, s, OCH_3), 4.28 ppm (2H, q, 3-CH_2), 5.00 ppm (1H, d, 6-H), 5.88 ppm (1H, dd, 7-H), 6.88 ppm (1H, s, ), 6.92 ppm (1H, d, CONH), 7.31 ppm (10H, s, ).

Example 10

A mixture of a solution of 160 mg of 3-oxo-2-ethoxyiminobutyric acid in 5 ml of methylene chloride with 250 mg of phosphorus pentachloride is stirred at room temperature for one hour to obtain a solution of the acid chloride. On the other hand, a solution of 330 mg of t-butyl 7-aminocephalosporanate and 240 mg of pyridine in 5 ml of methylene chloride is cooled to -50°C, at which the above acid chloride solution is added dropwise thereto and the mixture after completion of the dropwise addition is stirred at room temperature for 2 hours. The reaction mixture is mixed with 100 ml of ethyl acetate and washed with water, 3N-hydrochloric acid, water, 5% aqueous hydrogen carbonate solution and then with water, followed by drying. The residue obtained by evaporation of the solvent is subjected to purification by silica gel chromatography to give t-butyl 7-(3-oxo-2-ethoxyiminobutyrylamino) cephalosporanate. 340 mg.

NMR($CDCl_3$): 1.34 ppm (3H, t, $CH_2C\underline{H}_3$), 1.50 ppm (9H, s, $C(CH_3)_3$, 2.04 ppm (3H, s, CH_3COO), 2.37 ppm (3H, s, CH_3CO), 3.42 ppm(2H, q, 2-CH_2), 4.33 ppm (2H, q, $C\underline{H}_2CH_3$), 4.89 ppm (2H, q, 3-CH_2), 4.97 ppm (1H, d, 6-H), 5.83 ppm (1H, dd, 7-H), 6.84 ppm (1H, d, CONH).

Example 11

A solution of 235 mg of t-butyl 7-(3-oxo-2-ethoxyiminobutyrylamino) cephalosporanate in 10 ml of methylene chloride is warmed to 35°C and a solution f 88 mg of bromine in 3 ml of methylene chloride is added thereto. When the color of bromine begins to disappear, heating is stopped and stirring is continued at room temperature until substantial decoloration. After shaking the reaction mixture with ice-water, the methylene chloride layer is separated and washed with ice-water and dried. The residue obtained by evaporation of methylene chloride is purified by silica gel chromatography to give t-butyl 7-(4-bromo-3-oxo-2-ethoxybutyrylamino) cephalosporanate. 190 mg. This product is found to be identical with that of Example 5 with respect to NMR, etc.

Example 12

To a mixture of 7 ml of water and 7 ml of acetone is added 419 mg of 7-(4-chloro-3-oxo-2-hydroxyiminobutyrylamino) cephalosporanic acid. In the whole mixture is dissolved while stirring under ice-cooling 300 mg of sodium carbonate followed by dropwise addition of 600 mg of dimethyl sulfate to the resultant solution. After 30 minutes, 300 mg of sodium carbonate and 300 mg of dimethyl sulfate are further added to the mixture, and stirring is continued for additional 30 minutes. To the reaction mixture are added 20 ml of ice-water and pH is adjusted to 2.0 with 10% hydrochloric acid, and the mixture is extracted with etyl acetate. The extracted layer is washed with water, dried and concentrated to give powdery crude product of 7-(4-chloro-3-oxo-2- methoxyiminobutyrylamino) cephalosporanic acid. 280 mg.

NMR(δ_6-DMSO): 2.00 ppm (3H, s, CH_3COO), 3.50 ppm (2H, bs, 2-CH_2), 4.01 ppm (3H, s, OCH_3), 4.76 ppm (2H, s, $ClCH_2CO$), 4.81 ppm (2H, q, 3-CH_2), 5.11 ppm (1H, d, 6-H), 5.73 ppm (1H, dd, 7-H), 9.53 ppm (1H, d, CONH).

Example 13

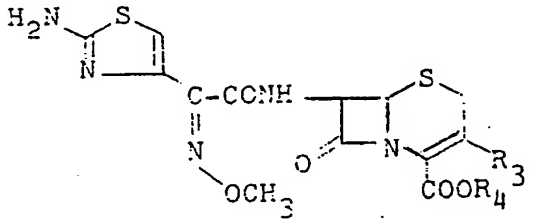
A mixture of a solution of 210 mg of 7-(4-chloro-3-oxo-2- methoxyiminobutyrylamino) cephalosporanic acid in 4 ml of N,N-dimethylacetamide with 100 mg of thiourea is stirred at room temperatue for 4 hours. To the reaction mixture is added 30 ml of ether and the precipitated oily product is separated by decantation.

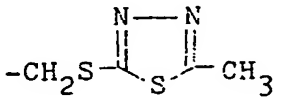
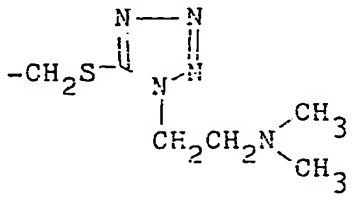
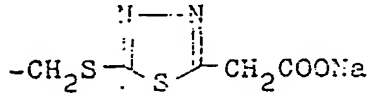
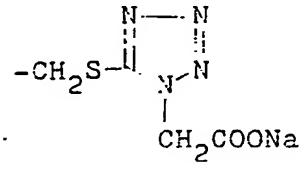
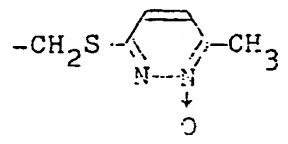
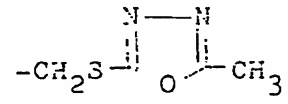
The oily product is dissolved in 5% aqueous sodium hydrogen carbonate solution and subjected to purification by column chromatography using Amberlite XAD-2 (registered trade mark: Rohm & Haas Co., U.S.A.) to give sodium 7-[2-(2-aminothiazol-4-yl) -2-(syn)-methoxyiminoacetamido] cephalosporanate as white power. 141 mg.

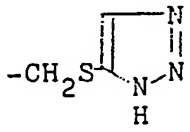
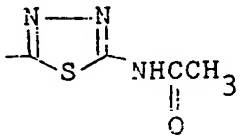
NMR(D_2O): 2.07 ppm (3H, s, $COCH_3$), 3.53 ppm (2H, q, 2-CH_2), 3.98 ppm (3H, s, OCH_3), 4.75 ppm (2H, q, 3-CH_2), 5.21 ppm (1H, d, 6-H), 5.81 ppm (1H, d, 7-H), 7.01 ppm (1H, s, thiazole 5-H).

Example 14

In the following Table, are shown examples of the compounds prepared according to the processes of the combination of Examples 12 and 13, the combination of Examples 7 and 8 and the combination of Examples 10, 11 and 6.



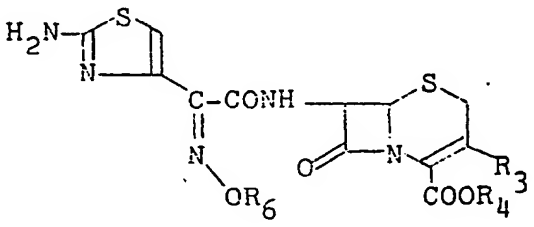
No.	R_3	R_4	NMR (solvent, ppm)
3		Na	D_2O; 2.57(3H,s,thiadiazole 2-CH_3), 3.52(2H,q,2-CH_2), 3.95(3H,s,OCH_3), 5.18(1H, d,6-H), 5.73(1H,d,7-H), 6.95(1H,s,thiazole 5-H)
4		Na	D_2O; 2.20(6H,s,$N(CH_3)_2$), 3.88(3H,s,OCH_3), 5.10(1H, d,6-H), 5.66(1H,d,7-H), 6.90(1H,s,thiazole 5-H)
5		Na	D_2O; 3.56(2H,q,2-CH_2), 3.96(3H,s,OCH_3), 4.18(2H, s,-CH_2COONa), 5.20(1H,d, 6-H), 5.74(1H,d,7-H), 6.97(1H,s,thiazole 5-H)
6		Na	D_2O; 3.55(2H,q,2-CH_2), 3.96(3H,s,OCH_3), 4.72(2H,s, -CH_2COONa), 5.18(1H,d,6-H), 5.72(1H,d,7-H), 6.95(1H,s, thiazole 5-H)
7		Na	D_2O; 2.60(3H,s,pyridazine 6-CH_3), 3.52(2H,q,2-CH_2), 3.98(3H,s,OCH_3),5.21(1H, d,6-H), 5.76(1H,d,7-H), 6.95(1H,s,thiazole 5-H)
8		Na	D_2O; 2.48(3H,s,oxadiazole 2-CH_3), 3.55(2H,q,2-CH_2), 4.02(3H,s,OCH_3), 5.13(1H, d,6-H), 5.73(1H,d,7-H), 6.97(1H,s,thiazole 5-H)

No.	R_3	R_4	NMR (solvent, ppm)
9			D_2O; 3.57(2H,q,2-CH_2), 3.94(3H,s,OCH_3), 5.21(1H, d,6-H),5.72(1H,d,7-H), 6.94(1H,s,thiazole 5-H), 7.95(1H,s,triazole 4-H)
10		Na	D_2O; 2.26(3H,s,$COCH_3$), 4.02(5H,bs,2-CH_2 and OCH_3), 5.37(1H,d,6-H), 5.92(1H, d,7-H), 7.01(1H,s,thiazole 5-H)
11	Cl	Na	D_2O; 3.60(2H,q,2-CH_2), 3.90(3H,s,OCH_3), 5.20(1H, d,6-H), 5.71(1H,d,7-H), 7.04(1H,s,thiazole 5-H)
12	OCH_3	Na	D_2O; 3.60(2H,q,2-CH_2), 3.76(3H,s,3-OCH_3), 4.01 (3H,s, >N-OCH_3), 5.24(1H, d,6-H), 5.66(1H,d,7-H), 7.06(1H,s,thiazole 5-H)
13	SCH_3	Na	D_2O; 2.10(3H,s,SCH_3), 3.62(2H,q,2-CH_2), 3.95(3H, s,OCH_3), 5.10(1H,d,6-H), 5.71(1H,d,7-H), 7.10(1H, s,thiazole 5-H)

s: singlet, D: doublet, t: triplet,
bs: broad singlet, q: quartet, m: multiplet,
dd: double of doublet

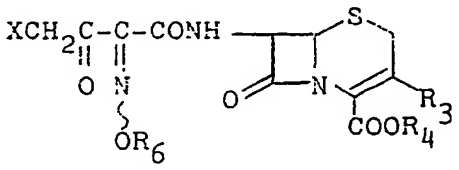
CLAIMS

1. A process for producing a 7-[2-(2-aminothiazol-4-yl) 2-(syn)-alkoxyiminoacetamido] cephalosporin derivative of the formula:



(II)

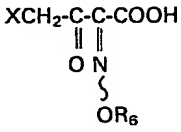
wherein R_3 represents $-CH_2R_5$ (R_5 is hydrogen atom or the residue of a nucleophilic compound), a halogen atom, an alkoxyl group, thiol group, amino group or  (Z is hydrogen atom or hydroxyl, amino, thiol or a hydrocarbon group which may be substituted), $-COOR_4$ represents a carboxylic group which may be esterified and R_6 represents an alkyl group, or a salt thereof, which comprises reacting 7-(4-halogeno-3-oxo-2-alkoxyiminobutyrylamino) cephalosporin derivative of the formula:



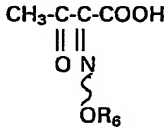
(I)

wherein X represents a halogen atom, R_3, $-COOR_4$ and R_6 have the same meanings as defined above, or a salt thereof with thiourea.

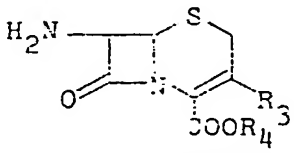
2. A process according to claim 1, wherein the 7-(4-halogeno-3-oxo-2- alkoxyiminobutyrylamino) cephalosporin derivative or a salt thereof is prepared by reacting a 4-halogeno-3-oxo- 2-alkoxyiminobutyric acid of the formula:



wherein X and R_6 have the same meanings as defined in claim 1, which is obtained by halogenating a 3-oxo-2-alkoxyiminobutyric acid of the formula:

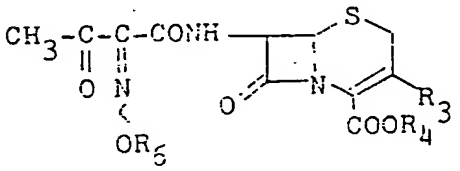


wherein R_6 has the same meaning as defined in claim 1, or a reactive derivative thereof, with a 7-aminocephalosporin derivative of the formula:

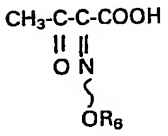


wherein R_3 and $-COOR_4$ have the same meanings as defined in claim 1, or a salt thereof.

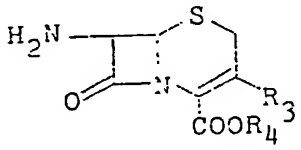
3. A process according to claim 1, wherein the 7-(4-halogeno-3-oxo-2-alkoxyiminobutyrylamino) cephalosporin derivative or a salt thereof is prepared by halogenating a 7-(3-oxo-2-alkoxyiminobutyrylamino) cephalosporin derivative of the formula:



wherein R_3, $-COOR_4$ and R_6 have the same meanings as defined in claim 1, or a salt thereof, which is obtained by reacting a 3-oxo-2-alkoxyiminobutyric acid of the formula:

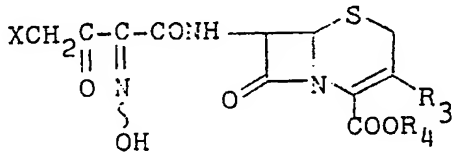


wherein R_6 has the same meaning as defined in claim 1, or a reactive derivative thereof, with a 7-aminocephalosporin derivative of the formula:



wherein R_3 and $-COOR_4$ have the same meanings as defined in claim 1, or a salt thereof.

4. A process according to claim 1, wherein the 7-(4-halogeno-3-oxo-2-alkoxyiminobutyrylamino) cephalosporin derivative or a salt thereof is prepared by alkylating a 7-(4-halogeno-3-oxo-2-hydroxyiminobutyrylamino) cephalosporin derivative of the formula:



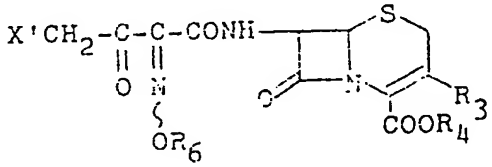
wherein X, R_3 and $-COOR_4$ have the same meanings as defined in claim 1, or a salt thereof.

5. A process according to claims 1 to 4, wherein the subject product is 7-[2-(2-aminothiazol-4-yl) -2-(syn)-methoxyiminoacetamido]-3-(1-methyl-1H-tetrazol-5-yl) thiomethyl-3- cephem-4-carboxylic acid.

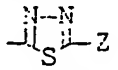
6. A process according to claims 1 to 4, wherein the subject product is 7-[2-(2-aminothiazol-4-yl) -2-(syn)-methoxyiminoacetamido]- 3-carbamoyloxymethyl-3-cephem-4-carboxylic acid.

7. A process according to claims 1 to 4, wherein the subject product is 7-[2-(2-aminothiazol-4-yl) -2-(syn)methoxyiminoacetamido] cephalosporanic acid.

8. A cephalosporin derivative of the formula:



wherein X' represents hydrogen atom or a halogen atom, R_3 represents $-CH_2R_5$ (R_5 is hydrogen atom or the residue of a nucleophilic compound), a halogen atom, an alkoxyl group, thiol group, amino group- or



(Z is hydrogen atom or hydroxyl, amino, thiol or a hydrocarbon group which may be substituted), $-COOR_4$ represents a carboxylic group which may be esterified and R_6 represents an alkyl group, or a salt thereof.

9. A process according to claim 1 substantially as described in any one of the foregoing Examples 1 to 14.

10. A cephalosporin derivative of the formula (II) as defined in claim 1, when prepared by a process according to any of claims 1 to 7 and 9.

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